REMARKS/ARGUMENTS

Status Of Pending Claims

Per Applicants' amendment of January 8, 2009 and the Office Action of April 15, 2009, claims 1-4, 7, 17-19, 22-31, and 33-41 were pending. Per this present amendment, claims 1-4, 7, 17-19, 22-31, and 33-41 are pending and presented for examination.

Amendments To The Claims

Claims 3 and 4 have been amended to recite a composition comprising the immunostimulating peptide of claim 1. Support for this amendment can be found in Applicants' application, e.g., in paragraphs [104] - [106] and Figure 1A and 1B, and in paragraphs [107], [110], and [131] to [135].

Claims 7 and 39-41 have been amended to correct punctuation.

Claims 28, 29, 36, and 37 have been amended for proper antecedent basis.

No new matter has been introduced by the present amendments.

Drawings

In the Office Actions mailed June 3, 2008, December 10, 2008, and April 15, 2009, the Examiner did not indicate whether the drawings as filed, including amended Figure 1B, are accepted as formal drawings or objected to by the Examiner. Applicants respectfully request such indication be made in the next office action.

Claim Rejection - 35 USC § 112, First Paragraph (Enablement)

The Examiner rejected claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner argued that allegedly (i) there is an art recognized lack of success for developing a HIV vaccine, (ii) Applicants' specification does not disclose any working embodiments for the claimed subject matter, and (iii) Applicants' disclosure fails to provide any guidance pertaining to the correlates of human protection. According to the Examiner, seemingly in view of the novel nature of

Applicants' invention, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

The rejection is respectfully traversed.

As the Examiner is aware, to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). Further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentations. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir), *cert. denied*, 484 U.S. 954 (1987).

Here, the Examiner seemingly argued that because no one succeeded in making a HIV vaccine, the subject matter of claims 3 and 4 is not enabled. Without acquiescing to the Examiner's argument, Applicants have amended claims 3 and 4 to recite "a composition comprising the immunostimulating peptide of claim 1" instead of a medicament comprising same. As disclosed in Applicants' application a composition comprising the immunostimulating peptide of claim 1 has been generated and used, e.g., in T2-binding assays (*see*, e.g., [paragraphs [104] - [106] and Figure 1A and 1B). Further, compositions comprising CTL peptides of the invention were used to immunize mice (*see*, e.g., paragraphs [107], [110], and [131] to [135]). These examples bear a reasonable correlation to the entire scope of the claim, and, thus, satisfy the enablement requirement of 35 U.S.C. 112. *In re Fisher*, 427 F.2d at 839.

Further, the Examiner did not reject claim 1 for lack of enablement. As such, in view of the art typically engaging in preparing compositions comprising biological materials,

such as peptides, more specifically, immunostimulating peptides, and claims 3 and 4 being directed to compositions comprising the immunostimulating peptide of claim 1, claims 3 and 4 are also enabled. *In re Wands*, 858 F.2d at 737. Even if some experimentation is required to make the composition of claims 3 and 4, such experimentation is routine and not undue. *In re Angstadt,* 537 F.2d at 504.

As such, Applicants provide sufficient disclosure, including working examples, to enable one reasonably skilled in the art to practice the claimed invention of a composition as recited in claims 3 and 4. One reasonably skilled in the art could make or use the invention from the disclosure in Applicants' patent application without undue experimentation.

Applicants respectfully request the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejection - 35 USC § 112, Second Paragraph (Indefiniteness)

The Examiner rejected claims 39 and 40 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner argued that while the claims reference immunostimulating polypeptides with X_1 and X_3 groups, they do not reference a corresponding X_2 group.

The rejection is respectfully traversed.

Claims 39 and 40 both depend from claim 7. Claim 7 recites a polypeptide having the sequence X_1X_2LYQYMDDVX_3 (SEQ ID NO:4) wherein X_1 is a sequence of amino acid residues of between 0 and 200 residues in length; X_2 is any hydrophobic amino acid; and X_3 is a sequence of amino acid residues of between 0 and 200 residues in length. (emphasis added)

Claims 39 and 40 recite a species of SEQ ID NO:4. Specifically, in claim 39, as shown by the sequence of X_1**V**LYQYMDDVX_3 (SEQ ID NO:5; emphasis added), X_2 is valine, a hydrophobic amino acid, abbreviated "V." Because V represents X_2, there is no need to further recite in claim 39 "wherein X_2 is V" or use any similar redundant language. Similarly, in claim 40, as shown by the sequence of X_1**Y**LYQYMDDVX_3 (SEQ ID NO:6, emphasis added), X_2 is tyrosine, a hydrophobic amino acid, abbreviated "Y." Because Y represents X_2, there is no need to further recite in claim 39 "wherein X_2 is Y" or use any similar redundant language.

As such, reading claims 39 and 40 in combination with claim 7 from which they depend, they define the metes and bounds of the patent protection desired.

Applicants respectfully request the rejection of claims 39 and 40 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections - 35 USC § 103

A. Harrer in view of Sarobe

The Examiner rejected Claims 1, 2, 7, 17, 30, 33-36, and 39-41 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Harrer [*sic*] *et al.* (1996; "Harrer") in view of Sarobe *et al.* (1998; "Sarobe"). Specifically, the Examiner argued that Harrer discloses a HLA-A2-restricted HIV-1 CTL epitope having the amino acid sequence IV**I**YQYMDD**L**, wherein the amino acid residues indicated in bold differ from Applicants' invention. The Examiner, thus, stated that Harrer does not disclose any of the immunostimulating peptides of the present invention having L2 and V9 substitutions with respect to the Harrer sequence.

However, the Examiner argued that Sarobe performed epitope optimization studies and demonstrated that substitution of the canonical anchor residues at positions 2 and 9 leads to a loss of CTL recognition. Allegedly, for HLA-A2 CTL epitopes these anchor residues are L2 and V9. According to the Examiner, it would be *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the HIV-1 CTL epitope of Harrer to include the canonical L2 and V9 anchor residues, because Sarobe allegedly demonstrated that these anchor residues are required for optimal MHC class I binding.

Applicants respectfully traverse.

Applicants herewith address the combined teaching of Harrer and Sarobe. First, Applicants agree with the Examiner that Harrer discloses a HLA-A2-restricted HIV-1 CTL epitope having the amino acid sequence IV**I**YQYMDD**L**, wherein the amino acid residues indicated in bold differ from Applicants' immunostimulating peptides of claims 1, 2, 17, 33, 34, and 36. However, the Examiner did not notice that when the Harrer sequence is compared to the amino acid sequence of the immunostimulating peptides of Applicants' claims 7, 30, and 35, additional amino acid changes in Applicants' immunostimulating peptides, such as having X_3

(claim 7) or having a tyrosine ("Y") at position 1 (claims 30 and 35) are apparent. Harrer does not disclose those sequences, nor does Sarobe. The Examiner does not discuss those amino acid differences in the Office Action of April 15, 2009.

Next, Applicants wish to point out to the Examiner that the natural peptide of Harrer, IV**I**YQYMDD**L**, which has isoleucine at position 2 of the minimal epitope (which begins with the V) and leucine at position 9 thereof, also binds to and is presented by HLA-A2 and is recognized by human T cells. Thus, this fact by itself would be *prima facie* evidence that L2 and V9, as present in Applicants' immunostimulating peptides, would not be required for binding, presentation, or recognition.

At the outset of the discussion of Sarobe, Applicants wish to point out that one of the inventors of the instant application, Jay A. Berzofsky, is the principal investigator of Sarobe and, thus, is familiar with the teaching of Sarobe.

Sarobe teaches studies for optimizing a CTL epitope from a conserved region of a Hepatitis C Virus core protein having the sequence D**L**MGYIPL**V** (C7A2). Accidentally, this CTL epitope has at amino acid position 2 a leucine (L2) and at amino acid position 9, a valine (V9). Sarobe describes this wild-type peptide, i.e, the peptide including L2 and V9, as having only intermediate affinity to HLA-A2.1 molecules (*see*, page 1241, left column).

In the studies described in Sarobe, peptides substituted with alanine at positions 1 through 9 were generated and analyzed. While alanine substitutions at positions 2, 6, 7, and 9 led to peptides with reduced binding affinity, Sarobe taught that alanine substitutions at positions 4 and 8 had higher binding affinity (*see*, page 1241, right column). Specifically, Sarobe stated in the abstract that:

> "A peptide with Ala substituted at position 8 (8A) showed higher HLA-A2 binding affinity and CTL recognition and was a more potent in vivo immunogen in HLA-A2-transgenic mice, inducing higher CTL responses with higher avidity against native C7A2 than induced by C7A2 itself. These results suggest that peptide 8A is more potent in vitro antigen and in vivo immunogen than C7A2 and may be useful as a vaccine component. They

> provide proof of principle that the strategy of epitope enhancement can enhance immunogenicity of a CTL epitope recognized by human CTL."

Thus, while Sarobe altered amino acid positions 2 or 9, Sarobe did not show the benefit of having L at position 2 and V at position 9 in an unrelated peptide (such as those claimed by Applicants) because those amino acid residues fortuitously were the amino acid residues at those positions in the wild type Hepatitis C Virus core protein sequence. All that Sarobe showed was that when L2 and V9 were altered a reduced binding was observed, similar to the alanine substitutions at positions 6 and 7. Thus, Sarobe did not "demonstrate that these anchor residues are required for optimal MHC class I binding" as alleged by the Examiner. Rather, Sarobe demonstrated that (i) substituting L2, I6, P7, and V9 in a peptide unrelated to Applicants' claimed immunostimulating peptide with alanine leads to a reduced HLA-2A binding and (ii) substituting positions 4 and 8 with an alanine leads to an improved peptide with respect to binding to HLA-2A.

One of ordinary skill in the art would appreciate from the teaching of Sarobe that 4A or 8A substitutions might be beneficial—not that L2, I6, P7, or V9 were beneficial in an unrelated peptide. Applicants' immunostimulating peptides do not have alanine at positions 4 or 8. In that respect, Sarobe may be considered teaching away from Applicants' claimed invention, because one of skill in the art would be motivated to incorporate A4 or A8 into a peptide and, thus, would not arrive at Applicants' invention. As the Examiner is aware, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir 1983).

Further, the test for obviousness is not whether the features of a secondary reference (here, the fortuitous presence of L2 and V9 in the Sarobe CTL peptide sequence) may be bodily incorporated into the structure of the primary reference (here, into the IVIYQYMDDL sequence of Harrer). Rather the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Further, given that Sarobe also showed reduced HLA-2A binding of peptides when substituting I6 and P7, the Examiner did not explain why one of skill in the art

would not choose those positions for an epitope enhancement or why one of skill in the art would choose L2 and V9 over I6 and P7. Combining the teaching of Harrer and Sarobe, one of skill in the art rather may be motivated to incorporate the "beneficial" substitutions taught by Sarobe into a peptide and make a peptide having the amino acid sequence IVIYQYMD**AL** (incorporating A8) or IVI**YA**YMDD**L** (incorporating A4) each of which differs from Applicants' claimed immunostimulating peptides in at least 3 amino acid positions (indicated in bold). The peptides obtained so may or may not have an immunostimulating activity.

Applicants believe that the rejection of claims 1, 2, 7, 17, 30, 33-36, and 39-41 has been addressed satisfactorily and respectfully request withdrawal of the rejection of these claims under 35 U.S.C. § 103(a), as allegedly being unpatentable over Harrer in view of Sarobe.

B. Harrer in view of Sarobe and further in view of Bolognesi

The Examiner rejected claims 18, 19, 24, 28, 29, and 37 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Harrer in view of Sarobe as applied *supra* to claims 1, 2, 7, 17, 30, 33-36, and 39-41, and further in view of Bolognesi *et al.* (2000, U.S. Patent No. 6,133,418; "Bolognesi").

Applicants respectfully traverse.

Claims 18 and 19 depend from claim 17, the subject matter of which, as demonstrated above, is patentable over Harrer in view of Sarobe and not obvious. Thus, claims 18 and 19 cannot be obvious further in view of Bolegnesi, which the Examiner cited for the mere disclosure of modifying a peptide at the N- or C-terminus for facilitating their conjugation to other macromolecular carriers. Further, Bolognesi does not disclose any peptides having a sequence similar to those claimed by Applicants.

Claims 24, 28, and 29 depend either directly or indirectly from claim 1, the subject matter of which, as demonstrated above, is patentable over Harrer in view of Sarobe and not obvious. Thus, claims 24, 28, and 29 cannot be obvious further in view of Bolegnesi for the reasons given above.

Claim 37 depends from claim 33, the subject matter of which, as demonstrated above, is patentable over Harrer in view of Sarobe and not obvious. Thus, claim 33 cannot be obvious further in view of Bolegnesi for the reasons given above.

Applicants believe that the rejection of claims 18, 19, 24, 28, 29, and 37 has been addressed satisfactorily and respectfully request withdrawal of the rejection of these claims as allegedly being unpatentable over Harrer in view of Sarobe, and further in view of Bolognesi.

C. Harrer in view of Sarobe and further in view of Berzofsky-A

The Examiner rejected claims 22, 23, and 25-27 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Harrer in view of Sarobe as applied *supra* to claims 1, 2, 7, 17, 30, 33-36, and 39-41, and further in view of Berzofsky *et al.* (1999; "Berzofsky-A").

Applicants respectfully traverse.

Claims 22, 23, and 25-27 depend either directly or indirectly from claim 1, the subject matter of which, as demonstrated above, is patentable over Harrer in view of Sarobe and not obvious. Thus, for the reasons given above, claims 22, 23, and 25-27 cannot be obvious further in view of Berzofsky-A, which the Examiner cited for the mere disclosure of preparing of cluster, or fusion polypeptides comprising CTL, humoral and T-helper HIV epitopes fused to one another. Further, Berzofsky-A does not disclose any peptides claimed by Applicants.

Applicants believe that the rejection of claims 22, 23, and 25-27 has been addressed satisfactorily and respectfully request withdrawal of the rejection of these claims as allegedly being unpatentable over Harrer in view of Sarobe, and further in view of Berzofsky-A.

D. Harrer in view of Sarobe and further in view of Berzofsky-B

The Examiner rejected claims 31 and 38 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Harrer in view of Sarobe as applied *supra* to claims 1, 2, 7, 17, 30, 33-36, and 39-41, and further in view of Berzofsky *et al.* (2001; "Berzofsky-B").

Applicants respectfully traverse.

Claims 31 and 38 recite as an additional feature that the immunostimulating peptide of claims 1 and 33, respectively, are pulsed onto dendritic cells. As such, claims 31 and 38 incorporate the subject matter of claims 1 and 31, respectively, the subject matter of which, as

demonstrated above, is patentable over Harrer in view of Sarobe and not obvious. Thus, for the reasons given above, claims 31 and 38 cannot be obvious further in view of Berzofsky-B, which the Examiner cited for the mere disclosure of utilizing peptide-pulsed dendritic cells for the development of strong anti-HIV immune responses. Further, Berzofsky-B does not disclose any peptides claimed by Applicants.

Applicants believe that the rejection of claims 31 and 38 has been addressed satisfactorily and respectfully request withdrawal of the rejection of these claims as allegedly being unpatentable over Harrer in view of Sarobe, and further in view of Berzofsky-B.

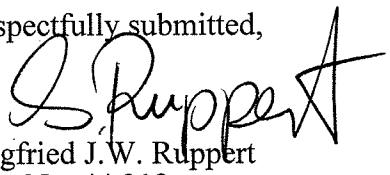
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition of allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fee is required. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from or credit any overpayment to, the above-noted Deposit Account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Siegfried J.W. Ruppert
Reg. No. 44,312

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
S1R:mcd

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